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Examiner allowed claims 8 and 9, and rejected the remaining pending claims based on 35 USC 112 issues. In the Final Office action, the Examiner concluded that "However, absent hindsight evidence, neither Graham et al., Mack et al., nor Kass-Eisler teach, suggest, or render obvious the use of *a series of helper adenoviruses of a [sic] different serotypes relative to the helper dependent vector* in combining these references." (Page 13, italics in original.)

In that Final action, the Examiner maintained 35 USC 112, second paragraph rejections of claims 1-4 and 13-15 based on allegedly indefinite phrases (detailed below). Applicants, on 11/16/2001, faxed a draft set of proposed amendments (and new claims) to overcome these and other rejections. In discussions with Examiner Brunovskis later the same day, no agreement was reached as to the suitability of the proposed amendments. Applicants believed they could provide a revised set of proposed amendments the following day (since time was of the essence as the Examiner was leaving the Patent Office employment the following week). However, discussions between the attorneys for Applicants and the lead inventor delayed a response until this response, filed late in the day on 11/19/2001.

It is respectfully requested that the amendments and new claim provided herein are entered. These amendments overcome all rejections in the Final action, correct other problems identified in the claims, and place the application in condition for allowance.

35 USC 112, second paragraph

Claim 1:

In the Final Office action, the Examiner maintained the rejection of the term "substantially devoid" based on alleged indefiniteness of Claim 1. The Examiner indicated that amending to recite "devoid", "completely devoid", or "lacking" would obviate the rejection. (Page 3)

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After careful review of the prior art references and the specification, the Applicants have amended Claim 1 to more clearly specify what the helper dependent adenovirus vector is devoid of. The application, on page 20, line 17, references Parks et al. (1996). Parks et al., which includes inventors of the present application, details the construction of a helper dependent vector, AdRP1001. (This and other cited publications are incorporated by reference per page 10, line 23.) Per that reference, pRP1001 "retained ~ 11.9 kb of Ad5 DNA" (page 13570). The related vectors exemplified in the specification, AdRP1045, AdRP1046 and AdRP1050, were produced in the same manner as pRP1001, but were designed, for the purposes of demonstrating less immune response, to contain fewer adenoviral protein coding sequences (see specification, page 20, lines 17-28).

Compliance with Examiner Bruovskis suggestion to amend the claim by modifying the term "substantially devoid" to "devoid", "completely devoid", or "lacking" while such terms modify the term "adenoviral protein coding sequences" is unduly restrictive and not consistent with scope of the invention as indicated by the Parks et al. reference. A helper dependent vector, such as AdRP1001, may contain sequences of adenoviral origin in addition to the right and left ITRs and the packaging signal, and still fall within the scope of the invention. For instance, it is noted that AdRP1045, contains at least 300 bp next to the right ITR.

Thus, it is not *any* adenoviral protein coding sequences that are "lacking" in the helper dependent vector of the present invention. Rather, it is adenoviral coding sequences that code for entire virion coat proteins, e.g., *adenovirion protein coding sequences*, that are lacking in the hdAd. It is these complete capsid proteins, encoded in different helper adenoviruses, that provides the invention with the key feature, namely, *a series of helper adenoviruses of different serotypes relative to the helper dependent vector*. This series allows the sequential administration of the same hdAd, which is encoded for a desired gene, such that the expression of that gene may persist for a longer period of time because there is a lesser immune response to a different capsid

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having different proteins (from the different helper adenoviruses in the series).

Therefore, the Applicants assert that the key to proper delineation of Claim 1 is to state that the helper dependent adenovirus vector in part (a) comprises a genome "lacking adenovirion protein coding sequences." This clarifies that the helper dependent adenovirus genome lacks adenoviral coding sequences that code for complete proteins of the virion capsule. As described above and in the specification in general, and on page 5, lines 8 and 9 in particular, this is an essential aspect of the invention (i.e., see page 5, lines 8 and 9, referring to one embodiment of the invention, stating that "... genetically identical hdAd [helper dependent adenovirus vector] that differ only in the virion protein components, which are derived from the helper virus, were produced." Also on page 5, lines 13-16, another object of the invention is "to provide a helper-dependent adenovirus vector (hdAd) administration system whereby repeat administration of a gene of interest is facilitated by using hdAd *wherein all protein present in said hdAd is derived from a helper virus*, the serotype of which is switched in the production of a vector to be used in a repeat hdAd administration." (Emphasis added.)

Thus, based on the Parks et al. reference and these quoted passages (and the specification in general), it is clear that the key aspect of a "lacking" in the hdAd is not the presence of *any* adenoviral coding sequences or adenoviral protein coding sequences (the minimization of which is understandably preferred, generally, to reduce anticipated immunogenicity to a protein expressed by such sequences in a recipient), but, critically, to adenoviral sequences that encode virion proteins, e.g., adenovirion protein coding sequences. Thus, from the aspect of properly defining the metes and bounds of the present invention, it is respectfully asserted that this proposed amendment of Claim 1 properly defines the claim limitations and overcomes the alleged rejection based on indefiniteness.

Further, Claim 1 as amended is not anticipated nor rendered obvious by the prior art of record. In

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fact, the basis of Examiner Brunovski's conclusion quoted above, that "absent hindsight evidence, neither Graham et al., Mack et al., nor Kass-Eisler teach, suggest, or render obvious the use of a series of helper adenoviruses of a [sic] different serotypes relative to the helper dependent vector in combining these references" (Page 13), is made more clear by the proposed amendment. It is clear that the series of different helper adenoviruses of different serotypes provide the adenoviral sequences that encode the proteins for the virion capsid. This is the basis for the ability to use the same core hdAd genome with different helper adenoviruses, having different serotypes (based on the sources of their protein coat sequences), to produce packaged vectors that can be used sequentially without eliciting adverse immune responses.

Therefore, Claim 1 as amended is not anticipated nor rendered obvious by either Graham et al., Mack et al., Kass-Eisler alone or in combination.

Another amendment to claim 1, part (b), is made although this is not directly to respond to the Examiner's rejection. This is the phrase "but which helper adenoviruses themselves do not package into infectious viral particles." It is clear, as from the specification, page 24, lines 5-7, that very low titres of helper virus may package (~0.02% of total packaged virus). Thus the specification is at odds with the plain meaning of the phrase. The now-deleted phrase is neither required for novelty nor functionality, and is properly removed to render the claim to properly define the invention.

Entry of Claim 1 as amended is respectfully requested.

Claim 13

In the Final Office action, claim 13 was rejected under 35 USC 112, second paragraph, for two reasons. First, the phrase "essentially no infectious particles of helper virus" in part (c) was identified by the Examiner as indefinite. The actual phrase in part (b) of the claim is "whereby

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little or no infectious particles of helper virus are present in the final hdAd stock." This phrase is removed as it is considered not necessary for novelty.

The specification teaches a superior method of obtaining helper-dependent vectors which results in very low levels of contaminating helper virus. However, the claimed method of making a series of genetically identical adenoviral vectors wherein each member of said series has a different serotype does in fact not rely for novelty on this superior method – other methods could be used, although these are expected to result in different, varying levels of contamination with helper virus, and/or require greater purification steps to achieve a desired level of purity. The preferred and alternative methods are discussed in the specification, from page 8, line 24 through page 10, line 6 (and particularly page 9, lines 18-27 – noting the described system is only preferred, and page 10, lines 4-6), and are further described in the references cited in this part of the specification.

In that this limitation is not necessary to define the functionality of the claim, nor to overcome prior art references, the Applicants have amended the claim to remove this phrase.

Claim 13 also was rejected as indefinite based on the limitation in part (c), "capsid proteins encoded by said helper adenovirus." The amendment in part (a) above is in accord with the Examiner's suggestion, page 3, last line, to page 4, line 2, of 07/18/2001 Office action, to overcome this basis for rejection.

It is noted that another phrase in claim 13, in part (b), could be interpreted under a similar basis as above rejections to be indefinite. This phrase is "but encoding little or no adenoviral gene products." Accordingly, for the reasons cited in the discussion for claim 1, above, this phrase has been amended to correctly recite the intended limitation, namely, "but not encoding adenovirion proteins."

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Entry of Claim 13 as amended is respectfully requested.

35 USC 112, first paragraph

Claim 15 was rejected under 35 USC 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." (Page 4)

The Applicants have amended claim 15 to delete the phrase, "and the serotypes of said at least two helper adenoviruses do not give . . . rise to a subject in need of said adenoviral vector gene delivery system." This is in accordance with the Examiner's suggestion on page 12 of the Final Office action to overcome this rejection. This amendment is made to expedite allowance of the claim as amended. For the record, the Applicants do not agree with the statements regarding lack of enablement of the claim as originally drafted. The Applicants have addressed many issues pertinent to this rejection in their 4/26/2001 Response. Since the amendment renders further discussion moot, it is merely asserted that the claim, as amended, is in condition for allowance.

Entry of Claim 15 as amended is respectfully requested.

Consideration of Issues under 37 CFR 1.116(c)

37 CFR 1.116(c) requires a showing of good and sufficient reasons why such are necessary and were not presented earlier, for admittance of amendments "touching the merits of the application." As to amendments made and discussed above that are not in direct response to a specific rejection in the 07/18/2001 Final Office action, these were made after extensive review of the claims in response to the specific rejections in the noted Final Office action. The subtleties of the reasons for making these additional amendments were not appreciated until this review

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following receipt of the Final Office action (and for some amendments, the need was not appreciated until the last two days prior to this submission, after communications with the Examiner and with the lead inventor). These amendments are considered necessary to properly define and claim the invention. It is respectfully asserted that admission of these amendments at this time will reduce unnecessary additional effort on the parts of both the Patent Office and the Applicants, in that the application clearly has allowable subject matter and the amendments place the claims in proper form and condition for allowance.

All grounds for rejection having been addressed and overcome herein, it is respectfully urged that this application is in condition for allowance. Should the Examiner be of the opinion that there remain valid grounds on which any of the pending claims, including those as herein amended, may be rejected, it is respectfully requested that the undersigned be accorded the courtesy of a telephonic or in-person interview to address and overcome any such remaining grounds for rejection.

Respectfully submitted,



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Attachment to November 19, 2001 Response to the Final Office action mailed July 18, 2001:

Marked-up claims.

Please make the following amendments in the following specified claims.

Claim 1: Please consider the following change(s) to claim 1:

- 1 (Amended). An adenoviral vector gene delivery system comprising:
- 2 (a) a helper dependent adenovirus vector, hdAd, comprising a genome
- 3 lacking[substantially devoid of adenoviral] adenovirion protein coding sequences, but
- 4 encoding a gene and expression control sequences, the expression of which in a
- 5 recipient cell is desired;
- 6 (b) helper adenoviruses of different serotypes encoding all functions required to facilitate
- 7 hdAd genome packaging and replication[, but which helper adenoviruses themselves
- 8 do not package into infectious viral particles]; and
- 9 (c) a cell into which may be introduced, in separate introduction steps, a helper adenovirus
- 10 of a first serotype and said hdAd, such that each said separate introduction step results
- 11 in the production of a packaged hdAd having the serotype of the helper adenovirus co-
- 12 introduced into said cell in said step.

15 Claim 13: Please consider the following change(s) to claim 13:

- 1 13 (twice amended). A method of making a series of genetically identical adenoviral vectors
- 2 wherein each member of said series has a different serotype, for delivering and expressing a
- 3 desirable gene in a recipient of said series of genetically identical adenoviral vectors which

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4 comprises:

5 (a) making a series of helper adenoviruses of differing serotypes, each serotype of said series
6 of adenoviruses encoding [expressing] a different set of capsid proteins;

7 (b) making a helper dependent adenovirus vector, hdAd, having a genome encoding said gene,
8 an adenoviral packaging signal, the adenoviral left ITR and the adenoviral right ITR and as
9 much additional nucleic acid sequences as are necessary to ensure expression of said gene and
10 packaging of said hdAd genome, but not encoding [little or no adenoviral gene products]
11 adenovirion proteins;

12 (c) generating a first stock of said hdAd *in vitro* by co-introducing into a cell said hdAd
13 genome and a helper adenovirus of a first serotype under conditions [whereby little or no
14 infectious particles of helper virus are present in the final hdAd stock, but] wherein said stock
15 is highly enriched in infectious particles comprising said hdAd genome and capsid proteins
16 encoded by said helper adenovirus of said first serotype;

17 (d) repeating step (c) as many times as desired using a helper adenovirus of a different
18 serotype each time said step (c) is repeated, such that a series of infectious hdAd stocks are
19 generated, with each said stock having said different set of capsid proteins based on said
20 different serotype; and

21 (e) recovering said infectious hdAd stocks having a capsid of different serotype to obtain said
22 series of genetically identical adenoviral vectors.

Claim 15: Please consider the following change(s) to claim 15:

1 15 (Amended). The adenoviral vector gene delivery system of claim 1 wherein, in a series of said
2 packaged helper dependent adenoviruses, at least two helper adenoviruses are from one subgroup
3 of adenoviruses; and the serotypes of said at least two helper adenoviruses do not give rise to

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- 4 cross reactive antibodies when administered to a subject in need of said adenoviral vector gene
5 delivery system].